Microbiological assessment of the concentration of cephacetrile in plasma and cancellous bone of femoral heads

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Sir,

We have been interested in the ability of the antibiotic, cephacetrile, in therapeutic concentrations, to enter bone tissue. Cephacetrile was administered in a dose of 0·5 g i.v. initially followed by constant infusion of 0·5 g/h for 4 to 18 h. The material used for our study consisted of the excised femoral heads from 15 patients who wese fitted with artificial hip-joints due to coxarthrosis. We are of course conscious of the negative selection of this material, since it is well known that coxarthrosis is accompanied by deficient circulation of the blood in the bone tissue. Nevertheless, following intravenous cephacetrile infusion lasting several hours, until the steady state was achieved, we have been able to demonstrate that cephacetrile reaches the bone in therapeutically adequate concentrations (Table I).

The method used is based on the microbiological determination of the concentration of the antibiotic in the cancellous bone of the head of the femur, after subtraction of the cephacetrile content of the blood in the cancellous bone.

The quantitative blood content of the homogenized bone substance was calculated via the determination of haemin, by a new procedure which has not yet been published.

Table I. Cephacetrile concentrations in plasma and in blood-free cancellous bone at the time of excision of the femoral head

Patient	Plasma (µg/ml)	Blood-free spongiosa (µg/g)	% of plasma
During the cephacetrile infusion			
A.A.	49·1	11·75	23·9
F.M.	46·75	6·92	14·8
R.B.	40·2	6·06	15·1
S.I.	38·8	2·54	6·6
B.I.	36·3	3·17	8·7
K.I.	32·8	2·45	7·5
S.L.	25·7	7·36	28·6
W.K.	25·0	5·23	20·9
K.H.	24·7	2·85	11·5
H.H.	15·3	3·47	22·7
S.G.	14·3	7·94	55·5
			$\bar{x} = 19{\cdot}6$
2 to 4·5 h after end of cephacetrile infusion			
B.H.	7·8	2·44	31·3
G.M.	4·75	~2·08	43·8
E.D.	4·7	~1·99	42·3
M.I.	4·0	~0·87	21·8
			$\bar{x} = 34{\cdot}8$

Blood content of the cancellous bone: 5 to 33 µl/g.

Table II. Cephacetrile concentrations in plasma-water and in bone-water (content in bone calculated on the total water content of the bone)

Patient	Concentration in plasma-water (µg/ml)	Concentration in bone-water (µg/ml)
A.A.	36·83	40·30*
F.M.	35·06	23·92
R.B.	30·15	15·95*
S.I.	29·10	16·04
B.I.	27·23	9·81
K.I.	24·6	10·39
S.L.	19·28	19·92
W.K.	18·75	14·71
K.H.	18·53	10·97
H.H.	11·48	11·79
S.G.	10·73	24·09*

*Values not directly comparable, since there was no steady-state in the plasma.

The deep-frozen bone was crushed at −80°C, homogenized with phosphate buffer and the cephacetrile content of the homogenized bone substance determined by the agar well method (*B. subtilis*). A standard curve was produced from a series of cephacetrile-concentration dilutions in antibiotic-free bone homogenate.

The concentration of cephacetrile in cancellous bone tissue (after subtraction of the cephacetrile content of the blood in the bone tissue), was, on average, one-fifth of the concentration in serum (Table I).

The elimination of cephacetrile from the cancellous bone tissue is slower than the elimination from the plasma because after the end of the infusion the concentration in the cancellous bone tissue, in relation to the concentration in the plasma, is higher than during the infusion.

To the question whether the cephacetrile is only distributed in the water of the bone, or is adsorbed, for example to the cancellous bone tissue, we can say that cephacetrile is only present in the water of the bone (see Table II).

To summarize, cephacetrile can be detected in the cancellous bone tissue in therapeutic concentrations. It is however not adsorbed to the cancellous bone tissue.

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In vitro activity of cefuroxime against *Treponema pallidum*

Sir,

Cefuroxime is a new parenteral broad spectrum cephalosporin antibiotic, active against a variety of Gram-positive and Gram-negative organisms (O'Callaghan, Sykes, Griffiths & Thornton, 1976).

A preliminary study was carried out to assess the *in vitro* activity of cefuroxime against *Treponema pallidum* by the immobilization test. Cerfuroxime was compared with penicillin G, whose activity is already known (Galla, Pagnes & Ferrari, 1965) and two other cephalosporins, cefazolin and cephacetrile.

The virulent Nichols strain of *Treponema pallidum* was cultivated by the intratesticular infection of 6 months old New Zealand white rabbits (Collart, Franceschini & Durel, 1971). The rabbits were killed 8 days after the infection and their testicles were removed aseptically and minced.

The spirochetes were suspended in Delacretatz medium by gentle shaking (Delacretatz, 1953) and incubated with serial dilutions of the drugs at 37°C in N_2 (95%) and CO_2 (5%) atmosphere.

The overnight cultures were checked for the motility of the spirochetes in the control suspensions; the anti-treponemic activity of the drugs was determined as the Minimum Concentration Immobilizing 100% of the microorganisms (MImC).

The data shown in Table I confirm the activity of penicillin G (Galla, Pagnes & Ferrari, 1965). Cefuroxime also showed a high level of activity—greater than cefazolin and cephacetrile.

Table I.—Minimum immobilizing concentration of β-lactam antibiotics against *Treponema pallidum*, Nichols strain

Antibiotic	MImC (μg/ml)
Penicillin G	0·0016
Cefuroxime	0·0125
Cefazolin	0·25
Cephacetrile	5·0

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The effect of antibiotics and acetohydroxamic acid on bacterial hydrolysis of urea

Sir,

Ammonia generated by intestinal bacteria and absorbed into the circulation is implicated in the genesis of the coma of hepatic failure (Schenker, Breen & Hoyumpa, 1974). The beneficial effects of antibiotics given to correct ammonia intoxication are generally attributed to their bactericidal action but Belding & Kern (1963) found that oxytetracycline inhibited jack bean urease, and for this reason suggested that it should be used in treatment. However, bacterial and plant ureases are not identical (Hase & Kobashi, 1967) and may differ in their sensitivities to antibiotics.

To determine whether some benefit may be obtained from antibiotic therapy as a result of anti-urease activity in addition to antibacterial activity we have compared the action of five antibiotics, and a potent urease inhibitor, acetohydroxamic acid on a bacterial urease.

Urease was prepared from *Proteus mirabilis* grown on blood agar base (Oxoid CM271) containing 2% urea. The bacteria were harvested in 0·1 M-sodium phosphate buffer pH 7·2 containing 0·37 g/l disodium EDTA, centrifuged at 4°C and resuspended in buffer. Cells were disrupted by ultrasonication, recentrifuged, and the supernatent put through an 0·45 μm millipore filter. Samples were tested for sterility and potency and stored at −20°C.

The antibiotics tested were neomycin sulphate, kanamycin sulphate, gentamicin sulphate, oxytetracycline and chloramphenicol sodium succinate. Solutions of antibiotics